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EXAMINER	
GOLLAMUDI, SHARMILA S	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,795	BERNDL ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Request for Reconsideration filed 12/27/04 is acknowledged. Claims 1-6 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claim 1 recites 0.5-25% of at least one active, 0.5-60% of at least one cyclodextrin, 15-98% of at least one polymeric binder, and 0-50% excipients. Applicant cites pages 4, 5, and 9 for support of the ranges. However, a careful review of the specification provides support for a range of 0.5-30% or 1-25% of at least one active (see page 5, lines 5-6) and not amended 0.5-25%. Page 4, lines 40-43 provides support for 5-99.5%, 10-98%, and 15-80% of at least one polymeric binder and not amended 15-98%. Lastly, page 9, lines 20-25 provides support for 0.1-90%, 0.5-70%, and 1-60% of at least one cylcodextrin and not amended 0.5-60%. Further, upon a review of the specification the recitation of "dialkyl sulfates" and "carbonyl chlorides" does not have support on the pages cited for support, i.e. 7-8.

If applicant contends support other than the cited pages, the applicant is requested to point to the specific page and line.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baert et al (6,365,188) in view of Stella et al (6,046,177) in further view of Murata et al (5,500,221).

Baert et al teach a solid mixture of cyclodextrin prepared via melt extrusion. The melt-extrusion mixture contains cyclodextrin and an active agent. See column 3, lines 26-40. Baert discloses that cyclodextrins increase the solubility of the insoluble drugs such as anti-fungals. Any suitable compound may be utilized provided that the drug does not decompose at high temperatures. See column 2, lines 45-60. Baert teaches melt-extrusion as the polymer extrusion technique wherein an active agent is embedded in one or more carriers. In this technique the active and excipients are molten in the extruder and hence embedded in the thermoplastic and

thermomelting polymers. See column 3, lines 26-40. Additionally, the mixture may contain additives such as instant polyethylene glycol. See column 4, lines 34-42. The process includes a) mixing the cyclodextrin with the active agent and additives, b) heating the mixture until melting of one of the components occurs, c) forcing the mixture through one or more nozzles, and d) cooling the mixture to obtain a solid product. See column 4, lines 15-25. Although, a temperature of 239 degrees Celsius is exemplified, Baert discloses that different temperatures may be applied and discloses the method of ascertaining the required temperature. See column 5, lines 1-12. The extruder has counterotating screw with different shapes. See column 5. The melt-extruded mixture is preferably prepared without water or a solvent. The preferred ratio of the active to cyclodextrin is 1:3. See column 7, lines 64 to column 8, lines 4 and examples.

Baert et al do not teach the instant amount of the polymer in the extrusion mixture or the molecular weight of the PEG. Additionally, Baert does not teach the instant temperature of 220 degrees Celsius.

Stella et al teaches controlled release forms of solid formulations containing sulfoalkyl ether cyclodextrin (SAE-CD). The controlled release formulation contains a core containing an active agent, at least on SAE-CD, at least one rate controlling modifier, and at least one pharmaceutical acceptable excipient. See column 6, lines 1-7. The core may be made by several methods including melt extrusion. Note example 10. The release rate modifier provides either a delayed, sustained, timed, or targeted release of the active agent. See column 27, lines 40-50. Stella teaches varying the ratio of the rate controlling modifier and the drug such as 10:1 and 5:1, determines the release rate. The rate control modifier (exemplified HPMC) is varied from 25% to 50%. See column 17. Further, Stella teaches the use of binders such as celluloses, polyethylene

glycols, polyvinylpyrrolidone, vinyl alcohol polymers, s in order to obtain suitable products. See column 27, lines 5-30. Some of the binders named also function as the release rate modifier. See column 27, lines 48-50. The binder is utilized in different proportions in different examples. Example 10 discloses a process utilizing melt extrusion wherein 2.5% of an active, 67.5% of SAE-CD, 10.5% PEG 6000, and excipients are melted at 60 degrees Celsius to form granules. Lastly, Stella et al disclose that major portion (lower limit 50% and preferably greater than 95%) of the SAE-CD is not complexed to the active agent (col. 12, lines 9-22).

Murata et al teach a sustained release suppository. Murata teaches the polymers that are utilized for adjusting the release rate of drugs are water-soluble polymers such as hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone, methylcellulose, etc. see column 3, lines 20-36.

It would have been obvious at the time the invention was made to combine the teachings of Baert et al, Stella et al, and Murata et al and utilize the instant water-soluble polymer PVP in the extrusion mixture of Baert et al. Firstly one would have been motivated to do so since Stella teaches the use of a rate controlling modifiers, such as exemplified HPMC and teaches certain polymer binders among which instant PVP and PEG are taught, control the release rate of the active to provide for a delayed, targeted, sustained, etc. dosage form. Therefore, one would have been motivated to add a polymer such as instant polymer, to modify the release rate of the dosage form.

Secondly, one would have been further motivated to look to Murata and utilize instant PVP since Murata teaches the functional equivalency of Baert et al's exemplified rate-releasing modifier HPMC and instant PVP. Therefore, one would have been motivated to utilize the

instant PVP with the expectation of similar results since the prior art teaches the functional equivalency of Baert's HPMA and PVP as polymers that adjust the release rate of drugs in a dosage form. Furthermore, Baert also states that the binders taught, among which PVP is taught, may also function as the rate controlling modifier; thus one would expect the instant PVP to act as a rate controlling modifier in Baert's dosage form.

Lastly, with regard to the temperatures, this is deemed to a manipulatable parameter that depends on the components and their melting point of each component. Further, Baert teaches that different temperatures may be applied and discloses the method of ascertaining the required temperature.

Response to Arguments

Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection. However, the merits of Baert et al will be addressed since the examiner has retained Baert has the primary reference.

The applicant argues that Baert only teaches PEG has a plasticizer and not a binder. Applicant argues that Baert et al teaches a composition "consisting essentially of" an active and cyclodextrin.

Firstly, the examiner acknowledges that Baert's PEG functions as a plasticizer and not as a binder. Thus, the examiner relies on the secondary reference to cure deficiency.

With regard to Baert teaching away from the use of other additives, the examiner points to page 5 wherein Baert's method is disclosed is:

a) mixing one or more cyclodextrins with the active ingredient or active ingredients

b) optionally mixing additives

c) heating the thus obtained mixture until melting of one of the components

d) forcing the thus obtained mixture through one or more nozzles

e) cooling the mixture till it solidifies

Therefore, it is clear that other additives, such as Stella's rate controlling modifiers, may be utilized without an adverse effect.

Furthermore, the examiner points out that although Baert's preferred embodiment is directed to a composition "consisting essentially of" an active and cyclodextrin, the broader disclosure allows for the incorporation of additives and excipients. Additionally, it is pointed out that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/58529 to Meerpoel et al in view of Klimesch et al (4,880,585).

Meerpoel teaches a water-soluble azole as broad-spectrum antifungals. The composition may be in the form of an oral or rectal composition obtained by melt-extruding mixtures of the inventive compound and one or more pharmaceutically acceptable water-soluble polymers. See page 27. The technique comprises the following steps: a) mixing the active and appropriate water-soluble polymers, b) optionally mixing blending additives, c) heating the obtained blend until a homogenous melt is formed, d) forcing the melt through one or more nozzles, and e) cooling the melt until it solidifies. See page 27. Suitable water-soluble polymers taught are cellulose derivatives, starches, polysaccharides, polyvinylpyrrolidone, and copolymers of PVP with vinyl acetate. See page 28. Further, instant cyclodextrins are also taught as suitable water-

soluble polymers. The ratio of the active to cyclodextrin is in the ratio of 1/5 to 5/1; however it can vary. See page 28.

Meerpoel does not specify the melting temperature or the amount of the water-soluble polymers. Additionally, the reference does not teach the use of molding calendars.

Klimesch et al teaches a method of continuous tableting using a molding calendar with opposite rollers (col. 1, lines 16-27). The reference teaches the use of instant polymeric binder (PVP and copolymers of NVP) and instant temperature (col. 2, lines 40-68). The reference teaches the preferable temperature is 60-130 degrees Celsius to be extrudable and the temperature may be reduced by utilizing a plasticizer. See column 3, lines 1-10. Klimesch teaches that the instant polymer is conventional and converts the pharmacological actives into paste to be extruded. The advantage of the process is it makes premixing unnecessary (col. 1, lines 28-34). The active agent may be incorporated in the amount of 01-95 and in particular from 30-70%. See column 4, lines 29-40. Various ratios of the active/polymer/auxiliary are taught in Table 1. For instance, the active may be in the amount of 50% and the polymer may be in the amount of 50%. See example 32. In particular, the composition contains an active and 30-100% of a NVP polymer. See claim 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Meerpoel et al and Klimesch et al and incorporate Klimesch's teachings into Meerpoel's. One would have been motivated to do so since Klimesch teaches that the water-soluble polymers taught in Meerpoel, i.e. PVP and NVP copolymers with vinyl acetate, are conventionally utilized in extrusion processes to make the composition into a paste and melt in the range of 60-130 degrees; thus meeting instant temperature limitation.

Further, Klimesch teaches various ratios of the active ingredient and polymer, optionally containing an additive. The manipulation of the active, polymer, and various additives is deemed to be obvious to one of ordinary skill in the art by following the guidance provided by the prior art.

Response to Arguments

Applicant's arguments filed 12/27/04 have been fully considered but they are not persuasive. Applicant argues that Meerpoel does not teach the combination of cyclodextrin, the instant binders, and an active. Applicant argues that Meerpoel teaches cyclodextrin as an alternative to the instant water-soluble polymers.

The examiner points out that Meerpoel teaches the use of one or more water-soluble polymers and both PVP and cyclodextrin are taught as water-soluble polymers. Note page 27. Therefore, there is a clear suggestion of utilizing more that one water-soluble polymer. Absent unexpected results demonstrating the rejection is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616

SSG

MICHAEL HARTLEY
PRIMARY EXAMINER

properly regulated. In the above operation, the coating material comprising a second thermomelting material optionally with an additive may be charged first in the container without pre-heating and then subjected to heating under rotation until a coating layer having a desired thickness is formed on each particle. The formation of the coating layer may be effected in two or more stages using a coating material(s) of the same or different composition(s).

When the coating layer reaches a desired thickness, the temperature of the container is lowered, for instance, to about 40° C. or less for cooling under rotation so that coated granules having hard and compact coating layers at the surfaces are obtained.

When desired, any other appropriate operation may be applied between the granulating step and the coating step as above. For instance, the formation of a coating film comprising talc on the surfaces of the non-coated granules may be effected after the granulating step and before the coating step. Such talc film coating is effective in enhancing the physical strength of the non-coated granules so that those granules are protected from from breakage or disintegration during coating. It is also effective in taking up the pharmaceutically active substance in a powder form completely so that its attachment onto the surfaces of the granules in the coating step can be avoided. Incorporation of a suitable disintegrating agent into talc is sometimes advantageous, because the release of the pharmaceutically active substance from the resulting granules is delayed for a certain period of time. For the film formation, talc may be used in an amount of about 1 to 30 % by weight, preferably of about 5 to 20 % by weight based on the weight of the granules

Practical embodiments of the invention are illustratively shown in the following Examples wherein % and part(s) are by weight unless otherwise indicated.

EXAMPLE 1 (Granulating)

Benexate hydrochloride/beta-cyclodextrin inclusion compound (i.e. TA 903) (40 parts), powdery polyethylene glycol 6000 (i.e. PEG 6000) having a particle size of 300 μm (48 mesh) or less (18 parts) and sugar powder (4 parts) were mixed together to make a uniform mixture. The mixture (150 g) was charged into an agitation type mixer ("Super-mixer" Type SM-5, manufactured by Kawata Seisakusho), and hot water was circulated through the jacket of the mixer, whereby the container of the mixer was heated to about 95° to 100° C. The agitation blade was started to rotate slowly, and when PEG 6000 was melted to wet the entire mixture, the rotation speed was raised to about 900 rpm so that the granulation started to give fine spherical particles. The spherical particles were rolled in the container, during which a mixture having the same composition as above (350 g) was portionwise added thereto so as to make the spherical particles grown. Water was introduced into the jacket of the mixer so that the container was cooled to a temperature below 40° C.

The thus obtained granules had the following size distribution:

Particle size (μm)	Amount (g)
more than 710 (24 mesh on)	22.2 (4.5%)
710–420 (24–35 mesh)	149.7 (30.4%)
420–150 (35–100 mesh)	302.0 (61.4%)
less than 150 (100 mesh pass)	18.1 (3.7%)
Total	492.0

EXAMPLE 2 (Granulating)

Granules having a particle size of 150 to 420 um (35 to 100 mesh) (150 g) as obtained in Example 1 were charged in the container of a mixer, and the agitation blade was rotated slowly. The temperature of the container was elevated to about 95° to 100° C. while slow rolling of the granules. When the surfaces of the granules began to melt, the rotation speed was raised, and a mixture having the same composition as used in Example 1 (350 g) was portionwise added thereto so as to make the spherical particles grown. Water was introduced into the jacket of the mixer so that the container was cooled to a temperature below 40° C.

The thus obtained granules had the following size distribution:

Particle size (μm)	Amount (g)
more than 710 (24 mesh on)	14.6 (3.0%)
710–420 (24–35 mesh)	323.3 (65.5%)
420–150 (35–100 mesh)	103.9 (21.1%)
less than 150 (100 mesh pass)	51.5 (10.4%)
Total	493.3

EXAMPLE 3 (Coating)

Stearyl alcohol (6 parts) and polyethylene glycol (i.e. PEG 4000) (4 parts) were mixed together, and the resultant mixture was heated at 80° C. for fusion, followed by agitation. After cooling, the solidified product was crushed and pulverized to make a premix having a particle size of 300 μm or less as a coating material. Using the premix, the following two coating compositions were prepared:

	Part(s)
First coating composition:	
Talc	2
Corn starch	2
Premix	1
Total	5
Second coating composition:	
Talc	2
Lubriwax	2
Premix	1
Total	5

The granules having a particle size of 420 to 710 μm (24 to 35 mesh) (250 g) as prepared in Example 1 or 2 were charged into the container of a mixer ("Super-mixer" Type SM-5) and rotated slowly under agitation, whereby the granules were rolled. Hot water was circulated in the jacket of the mixer, and the temperature of the container was elevated to about 60° C. Then, the rotation speed was raised, and the first coating composition (150 g) was portionwise added thereto so as to coat the granules. Then, water was introduced into the jacket of the mixer to lower the temperature of the container below 40° C.

The coated granules thus obtained had a particle size of 420 to 1,000 μm (16 to 35 mesh) and a total weight of

Amt of cyclodextrin and achve prior to making inclusion complex not taught.

β-cyclodextrin) is dissolved in 900 ml of water while being stirred at 45° C. The ethanolic ethinylestradiol solution is added in drops to aqueous cyclodextrin solution within 40 minutes while being stirred, so that a slightly cloudy solution develops. Within 2 hours, the solution is cooled to 25° C. It is stirred for another 20 hours to 25° C. The precipitated solid is suctioned off and washed twice with 50 ml of water each. The crystallizate is suspended twice with 40 ml of acetone each and suctioned off. Then, it is rewashed with 50 ml of water. The wet crystallizate is dried in a vacuum with phosphorous pentoxide.

The content of 17α-ethinylestradiol in the inclusion bond is determined by means of high-pressure liquid chromatography and is 10.2%.

EXAMPLE 2

2.37 g of β-cyclodextrin is dissolved in 200 ml of water. 118.6 mg of 17α-ethinylestradiol is weighed into the aqueous cyclodextrin solution. The suspension is stirred for 48 hours. The solid is suctioned off and washed twice with 25 ml of water each. The crystallizate is suspended twice with 20 ml of acetone each and suctioned off. Then, it is rewashed with 20 ml of water. The wet crystallizate is dried in a vacuum with phosphorous pentoxide.

The content of ethinylestradiol in the inclusion bond is determined by means of high-pressure liquid chromatography and is 10.4%.

EXAMPLE 3

A β-cyclodextrin inclusion complex (produced according to Example 1) is ground and triturated in portions with lactose. Corn starch and modified starch are mixed in. The powder is processed into a granulate in a fluidized-bed granulator with an aqueous polyvinylpyrrolidone 25000 solution. After magnesium stearate is mixed in, the press dust that is obtained is pressed into tablets with a weight of 55 mg and a diameter of 5 mm.

Composition of a Tablet:	
Ethinylestradiol/β-cyclodextrin inclusion compound ≡ 10 μg of 17α-ethinylestradiol	0.098 mg
lactose	35.102 mg
corn starch	9.900 mg
modified starch	6.600 mg
polyvinylpyrrolidone 25000	2.750 mg
magnesium stearate	0.550 mg
	55,000 mg

EXAMPLE 4

A β-cyclodextrin inclusion complex (produced according to Example 2) is ground. 9.615 g of the complex (corresponding to 1 g of ethinylestradiol) is homogeneously added to a powder mixture that consists of 2360.385 g of lactose, 1300 g of microcrystalline cellulose, and 310 mg of corn starch. After 20 g of magnesium stearate is added, the powder press dust that is obtained is pressed with a tablet press into tablets with a 6 mm diameter and a tablet weight of 80 mg. They come with an active ingredient content of 20 μg of ethinylestradiol per tablet.

We claim:

1. A pharmaceutical composition comprising an effective amount of 17α-ethinylestradiol, and an amount of a β-cyclodextrin which is effective in reducing the oxidative degradation of the 17α-ethinylestradiol, wherein the composition is a clathrate.

2. A composition of claim 1, wherein the composition comprises about 10% w/w of 17α-ethinylestradiol to β-cyclodextrin.

3. A composition of claim 1, wherein the amount of 17α-ethinylestradiol is 0.01 μg–200 μg.

4. A composition of claim 1, wherein the amount of 17α-ethinylestradiol is 0.1 μg–200 μg.

5. A composition of claim 1, wherein the amount of 17α-ethinylestradiol is 10 μg–20 μg.

6. A composition of claim 1, wherein the 17α-ethinylestradiol is an inclusion in the β-cyclodextrin.

7. A method of reducing oxidative degradation of 17 α-ethinylestradiol comprising combining an amount of 17 α-ethinylestradiol and an amount of β-cyclodextrin which is effective in reducing the oxidative degradation of said estradiol.

8. The method of claim 7, wherein the 17 α-ethinylestradiol and the β-cyclodextrin are in a 1:1 mole:mole ratio.

9. The method of claim 7, wherein the amount of 17 α-ethinylestradiol is 0.01 μg–200 μg.

10. The method of claim 7, wherein the amount of 17 α-ethinylestradiol is 0.1 μg–200 μg.

11. A method of making a pharmaceutical composition, comprising an effective amount of 17α-ethinylestradiol and an amount of a β-cyclodextrin which is effective in reducing the oxidative degradation of the 17α-ethinylestradiol, wherein the composition is in a solid dosage form,

comprising, combining an amount of 17 α-ethinylestradiol and an amount of β-cyclodextrin which is effective in reducing the oxidative degradation of said estradiol.

12. The method of claim 11, further comprising dissolving the 17 α-ethinylestradiol in a suitable solvent, dissolving the β-cyclodextrin in an aqueous solution, combining said solutions of 17 α-ethinylestradiol and β-cyclodextrin, and isolating the resulting precipitated clathrate.

13. The method of claim 11, further comprising dissolving the β-cyclodextrin in an aqueous solution, adding solid 17 α-ethinylestradiol to said aqueous solution, and isolating the resulting clathrate.

14. A method of achieving an estrogenic effect comprising, administering a pharmaceutical composition, comprising an effective amount of 17α-ethinylestradiol and an amount of β-cyclodextrin which is effective in reducing the oxidative degradation of the 17α-ethinylestradiol, wherein the composition is in a solid dosage form.

* * * * *

Ex 1

42.48% - 20.96 active

57.52% 28.38 cyclodextrin

.0416 mg active → .0756%

.0563 mg cyclo. → 1.10%